SUBMISSION OF PROPOSAL FOR TOPIC APPROVAL IN THE FACULTY OF SCIENCE AND TECHNOLOGY

PROPOSAL FOR TOPIC APPROVAL TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE Ph.D. DEGREE IN THE SUBJECT OF **PHARMACEUTICS**.

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INDEX

Sr. No.	Contents	Page No.
1	Title	3
2	Aims of study	3
3	Objectives of Study	3
4	Study Background (Literature Review) and significance of study	3-4
5	National Status	4-6
6	International Status	6-7
7	Study Hypotheses	7-8
8	Study Rationale	8
9	Research Methodology	8-12
10	Statistical Plan	12-13
11	Limitations of the Study	13
12	Expected Outcomes of Study	13-14
13	Select Bibliography	14-15

1 Title

“Design and Evaluation of carrier system for improved delivery of an Antitubercular drug”

2 Aims of study

To design and develop drug delivery systems such as nano/microparticles to improve delivery of antitubercular drug.

3 Objectives of Study

The objective of the present study is to formulate drug loaded nano/microparticles for improved delivery of the drug in treatment of multi-drug resistant tuberculosis.

- To formulate, optimize and characterize antitubercular nano/microparticles systems.
- To compare the drug efficacy between oral route and pulmonary route of administration.
- To improve the efficacy and drug loading capacity of antitubercular drug by formulating nano/microparticles systems.
- To evaluate cytotoxicity of formulation by in-vitro cell culture study
- To study pharmacokinetic parameters.

4 Study Background (Literature Review) and significance of study

Tuberculosis is one of the leading causes of death across the globe. Tuberculosis (TB) is a disease caused by bacteria that are spread from person to person through the air. Antitubercular drug therapy currently faces a number of difficulties, a lack of solubility, including drug resistance, and a lack of selectivity. Each day, nearly 4000 lose their lives to TB and close to 28,000 people fall ill with this preventable and curable disease. According to the World Health Organization’s in 2021, an estimated 10.6 million people fell ill with tuberculosis (TB) worldwide. Six million men, 3.4 million women and 1.2 million children. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. Only about one in three people with drug resistant TB accessed treatment in 2020. In some countries, it is becoming increasingly difficult to treat MDR-TB. In some cases even more severe drug-resistant TB may develop. Treatment options or fewer medicines are limited and expensive, recommended medicines are not always available, and patients experience many adverse effects from the drugs. Fewer medicines which are available are

poor water soluble and low bioavailability. Attempt had been made to improve the drug solubility by complexation with cyclodextrin or formulating amorphous solid dispersion (1-2).

Due to the various benefits of the carrier based drug delivery systems, including biocompatibility, greater drug loading capacity, simplicity and safety of manufacture, fewer side effects, and enhanced efficacy, it has the potential to be used in the creation of novel medications. Nanoparticle and microparticle systems have the power to enhance poorly water-soluble medications' solubility, dissolution, side effects, and effectiveness. Therefore, it is imperative to create reliable ncarrier systems for antitubercular medications.

5. National Status

India faces a lot more difficulties in the treatment of multi drug resistance tuberculosis. Lack of access to the most efficient, secure, and cost-effective drug delivery for tuberculosis treatment is a major problem in India. Polymeric nanoparticles, microsphere, nanostructured lipid carrier, liposomes, nanocochleates, nanosuspensions, etc. are examples of carrier systems that have the ability to solve the problems associated with tuberculosis. In India, there is enormous potential for the development of antitubercular drug delivery systems with increased efficacy, biocompatibility, bio distribution, and reduced toxicity

Ayesha Gazi, et.al. (RBVRR Women's College of Pharmacy, Osmania University, Barkatpura, Hyderabad, India.) formulated and optimized methotrexate loaded polymeric nanoparticles. By using the nanoprecipitation process, methotrexate-loaded nanoparticles were created using Eudragit® S 100 and ethyl cellulose. Distinct drug to polymer ratios (1:1, 1:1.5, 1:2, 1:3, 1.5:1, and 2:1) were used to create six different formulations (f1, f2, f3, f4, f5, and f6) with each polymer. Dimethyl sulfoxide (DMSO) was the solvent used, while Tween® 20 was the surfactant. Out of the six formulations of polymeric nanoparticles produced by the nanoprecipitation technique, the F4 formulation was judged to be the best formulation with each polymer. Eudragit® S 100 was shown to be the most suitable polymer based on comparative findings of mean particle diameter, zeta potential, drug content, and entrapment efficiency for the production of methotrexate-loaded nanoparticles utilising the nanoprecipitation technique. Based on the evaluation tests, the ideal formulation's anti-cancer efficacy in the MCF-7 cell line was evaluated using the MTT assay, SEM, particle size, zeta potential, and scanning electron microscopy (SEM) (3).

Rajesh Pandey and G. K. Khuller (Department of Biochemistry, Postgraduate Institute of Medical Education & Research, Chandigarh—160 012, India) To lower dose/dosing frequency in the treatment of tuberculosis (TB), which otherwise necessitates protracted chemotherapy, alginate-chitosan microspheres as drug carriers are being developed. Three frontline anti-tuberculous medicines (ATDs), rifampicin, isoniazid, and pyrazinamide, were encapsulated in alginate-chitosan microspheres. The microsphere-encapsulated ATDs were given orally to guinea pigs for pharmacokinetic/chemotherapeutic studies at therapeutic and half-therapeutic doses. With a dosage of 220-280 mg of medicine per gramme microspheres, the drug encapsulation effectiveness varied from 65% to 85%. The microspheres were given orally to guinea pigs, who had maintained drug levels in their plasma and organs for 7 and 9 days, respectively. By encapsulating the medications in microspheres, the half-life and mean residence time of the pharmaceuticals were raised 13 to 15 times, and their relative/absolute bioavailability was improved. A subtherapeutic dosage of the microspheres likewise showed the prolonged release and rise in bioavailability. In guinea pigs infected with Mycobacterium tuberculosis H37Rv, the administration of therapeutic doses of microspheres spaced 10 days apart resulted in bacilli being cleared for 6 weeks, comparable to standard therapy (4).

Pankaj Goyal and S. Gill (Nanomedicine Research Centre, Department of Pharmaceutics, Indo-Soviet Friendship College of Pharmacy, Moga (Punjab), India) To prolong stomach retention duration, rifampicin floating microspheres were created. The microspheres were made using a solvent evaporation procedure, and their zeta potential, shape, entrapment, and release kinetics were all measured. The systems that were created have virtually spherical shapes. The entrapment efficiency was found to be 86.34%. After eight hours, the percentage buoyancy was discovered to be 61.06. Since the produced microspheres showed extended drug release in gastric medium, they might be used to administer anti-tubercular medications over time. (5).

B. Saisri, et.al. (KGR Institute of Technology and Management, Rampally, Kesara, Medchal, Telangana, India) created nanoparticles of the hydrophilic medication pramipexole dihydrochloride to increase the drug's ability to be captured. PLGA and Pluronic F68 were used to create the pramipexole dihydrochloride nanosuspension using a modified nanoprecipitation approach. The following measurements were made: particle size, zeta potential, SEM, TEM, and in vitro dig release. The SH-SY5Y cells were used for the cell viability investigation. Various

PLGA concentrations are used to create nano-formulations. Particle size and the effectiveness of drug entrapment in nanosuspension were shown to be significantly influenced by formulation factors such polymer concentration (PLGA). With a 1:3 ratio and 1% concentration of Pluronic F 68, the best invitro drug release profile, lowest particle size, and highest entrapment efficiency were demonstrated.. The least particle size of 195 nm and maximum zeta potential value 34.8 mv were observed with PPNP 3 formulation. When compared to other formulations, the SEM, TEM, and in vitro drug release of PPNP 3 demonstrate spherical shape with controlled release. Additionally, the MTT experiment was carried out using SH-SY5Y cells, which reveals that the PPNP 3 Nano formulation has higher cell viability when compared to the pure medication. The most effective formulation among the others is PPNP 3. As a result, the biodegradable polymer affects improved distribution of the Parkinson's disease medication in the brain. (6).

6. International Status

The field of novel drug delivery systems is one that is quickly developing because it offers solutions to a number of problems with traditional drug delivery. This is especially true for illnesses like tuberculosis, which present a number of difficulties. There have been more patents on nanoparticulate drug delivery in tuberculosis treatment as a result of the majority of research using nanoparticulate in recent years yielding encouraging results.

Usama Farghaly Aly et.al, (Department of Pharmaceutics, Faculty of Pharmacy, Minia University, El-Minia, Egypt) Simvastatin (SIM) polymeric nanoparticles (PoNPs) were incorporated into a hydrogel to increase the drug's solubility and skin penetration during topical wound healing. The polymeric nanoparticles were created using the nanoprecipitation process, and their drug concentration, solubility, particle size, and surface charge were assessed. They were also examined using transmission electron microscopy to examine hydrogel permeability in vitro and ex vivo. The polydispersity index was #0.302, the zeta potential was 331.67 mV, and the particle size was 268.4±2.6 nm. The hydrogel containing SIM PoNPs was uniform, and the pH was acceptable and skin-friendly. Additionally, the viscosity and spreadability guaranteed its simplicity of use.. The drug content was 97.25±0.02%. Furthermore, about 81% of SIM was released within 24 hours, while in the ex vivo permeation study 69.19% of SIM passed through the skin after 24 hours. Finally, the histopathological studies confirmed the efficacy of the SIM PoNPs-loaded

hydrogel in wound healing due to the formation of the normal epithelial layer on day 11 after wound creation (7).

Keiji Hirota, et,al (Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki Noda, Chiba 278-8510, Japan) formulated Rifampicin-loaded poly(lactic-co-glycolic acid) microspheres (MS) that are delivered to alveolar macrophage (M) cells by inhalation may be a successful medication delivery method for the treatment of TB. On Mycobacterium bovis Bacillus Calmette-Guérin (BCG)-infected rat alveolar M NR8383 cells, RFP-PLGA MS had a bactericidal effect, and its absorption altered the biochemical processes in these cells. The viability of M cells was not significantly impacted by RFP-PLGA MS compared to the polystyrene latex (PSL) MS that was utilised as a reference. Tumor necrosis factor (TNF), nitric oxide, interleukin-10 (IL-10), and transforming growth factor (TGF-1) production by the M cells was not activated by RFP-PLGA MS, whereas PSL MS stimulated all of these mediators with the exception of IL-10. We conclude that RFP–PLGA MS are bio-safe microspheres due to their "silent" nature when taken into Mϕ cells and that they are promising for the treatment of tuberculosis by pulmonary inhalation (8).

Salma M Mohyeldin, et.al (Department of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt) investigated the impact of new rifampicin nanosuspension (RIF NS) on improving medication delivery qualities. Using the antisolvent precipitation method, RIF NS was created. On its controlled nanocrystallization, the effects of the solvent-antisolvent volume ratio, stabiliser type and concentration, stirring duration and apparatus, and solvent type and flow rate have all been assessed. With a negative zeta potential and nanometer-sized particles (101 nm), nanocrystals were produced (-26 mV). RIF was 50 times more soluble in NS, and 97% of it was gone after just 10 minutes. The zeta potential and particle size of the RIF NS did not change much at 40.5°C. With half maximal inhibitory concentration values of 0.5 and 0.8 mg/mL for free RIF and RIF NS, respectively, the MTT cytotoxicity assay of RIF NS showed an excellent safety profile and decrease in cell cytotoxicity. A new RIF NS might be used as a strategy for improving RIF physicochemical properties, with a focus on safer and more effective drug delivery. (9).

7. Study Hypothesis

In comparison to conventional drug delivery systems, nano/microparticle systems have been proven to be more effective, safer, and important in the treatment of a variety of disorders. This is

particularly true for medicines used to treat tuberculosis, an infectious disease that can affect the lungs and other organs. Additionally, a lot of antitubercular drugs have issues that could reduce their bioavailability, such as decreased water solubility, pre-systemic metabolism, and gastrointestinal instability. By creating drug delivery methods like nano/microparticle systems, these issues can be partially resolved. The development of nanocarrier systems for medications like rifampicin, Isoniazid, pyrazinamide, streptomycin, clofazimine, and gentamicin in recent years has produced promising results and demonstrated a sound strategy to increase drug bioavailability, efficacy, and safety in a variety of disease treatments, particularly in cancer chemotherapy. According to a study, it is urgent to develop and evaluate nano/microparicle systems that have been loaded with antitubercular drugs.

8. Study Rationale

Multidrug-resistant TB (MDR TB) is caused by an organism that is resistant to at least isoniazid and rifampicin, the two most potent anti-TB drugs. These drugs are used to treat all persons with TB disease. Hence there was a need for a novel TB drug which can treat MDR TB. World Health Organization (WHO) approved a new TB drug belong to BCS Class II or IV with a novel mechanism of action for treatment of multidrug-resistant tuberculosis (MDR-TB), a form of tuberculosis resistant to at least isoniazid and rifampicin, the main first-line drug. However, the drug is poorly water soluble, degradation at high pH, melting point is quite high, toxicity, and oral bioavailability is also less. Much research has shown that carrier based systems has successfully been used to improve the pharmacokinetics of a pharmaceutical drug but also attributes like improve solubility, sustained release, increased half-life, higher drug concentrations at target sites, reduced toxicity and lesser side effects due to dose reduction.

9. Research Methodology

A. Characterization of drug and excipients

I) Spectroscopy Studies

1. Determination of Absorption Maxima
2. Analytical Method Development and Validation parameters

II) Identification of drug and excipients

III) Preformulation Studies

1. Solubility

2. Melting Point
3. Compatibility studies
4. Crystalllinity studies

B. Molecular Docking

Molecular docking is performed to calculate the binding energy between the drug and the excipient using appropriate software. The programme helps in pre-calculating the interaction between drug and polymer and also the binding interaction between them.

The stability was deliberated on the basis of interaction energy between the ligand and receptor. The more negative the score the better will be the binding.

C. Formulation Development

- **Preparation of Polymeric nanoparticles**
  1. Emulsion solvent evaporation method: Polymer and drug were dissolved in organic phase (internal phase) and is added in aqueous solution containing surfactant (external phase) under stirring. Resulting nanoparticles is kept on stirring to evaporate organic solvent. Centrifugation is done to form pellet. The formed nanoparticles were freeze dried or spray dried (10).
  2. Double emulsification method: Polymer and drug were dissolved in organic solvent and are added in aqueous solution under stirring or homogenizer to form primary emulsion. Another polymer solution is added in the primary emulsion under stirring or homogenizer to form w/o/w emulsion. The formed nanoparticles were freeze dried or spray dried (11).
- **Preparation of Microspheres**
  1. Solvent evaporation method: Drug is dissolved in organic phase. Polymer dissolved in aqueous phase or organic phase based on solubility with or without surfactant. Aqueous phase is injected into the organic phase drop wise or vice- versa under mechanical stirring. The microspheres were kept for some time under stirring to remove organic solvent. The particles should be collected by filtration, washed with water, and desiccated at room temperature (12).
  2. Emulsion solvent diffusion method: The polymer and drug should be dissolve in a

solvent mixture of organic solvent. Then, the dispersion solution added drop-by drop into polymer solution containing surfactant. Resultant emulsion stirred at room temperature for some time to remove organic solvent. The microspheres were separated by filtration, washed with water and dried at room temperature in a desiccator for 24 hour (13).

- **Preparation of Nanosuspension**
    1. Solvent-Antisolvent precipitation method: Drug will be dissolved in organic solvent. Organic phase drop wise addition into aqueous phase containing polymer with or without stabilizer under continuous stirring at a certain speed. Resulting suspension should be homogenize or sonicate for certain time (14).
    2. Nanoprecipitation method: Drug and polymer dissolve in organic phase. Organic phase injected slowly into an aqueous solution containing stabilizer under high speed mechanical agitation to get desired nano dispersion. Nanosuspension should be stirred for overnight to evaporate organic solvent. The volume adjusted with aqueous phase (15).

C. Optimization of Formulation:

Design-Expert software will be used to optimize critical formulation and process factors. All the process parameters affecting the productivity and quality of the formulation development process shall be optimized either by step by step approach or suitable design method. For attainment of desired properties such as high drug encapsulation efficiency, optimum particle size, polydispersity index, controlled drug release pattern both the processing conditions such as stirring time, speed, rate, etc. and formulation parameters such as active and excipient concentrations, will be optimized.

D. Characterization:

1. Yield and Drug content: Assay of drug in the NDDS can be calculated and how much is the batch production that can be calculated.
2. Particle size: Particle size is important parameter which can decide whether the NDDS is in micro or nano range.

3. Zeta potential: The potential difference existing between the surface of a particle immersed in a conducting liquid and the bulk of the liquid was analyzed. Overall it indicates the stability of formulation.
4. Encapsulation efficiency: How much amount of drug is entrapped in the carrier can be calculated
5. Surface morphology by Scanning electron microscopy (SEM): Shape of the particle in the formulation can be estimated.
6. Transmission electron microscopy (TEM): Shape of the particle in the formulation can be estimated.
7. Fourier transform infrared spectroscopy: Various bonds between drug and carrier or excipient can be identified. Overall it gives the interaction between drug and excipients in the NDDS and can be compare with free drug and excipients.
8. Differential scanning calorimetry (DSC): Melting point of the drug and other excipients can be determine. Also stability of the formulation can be predicated too.
9. X-ray diffraction (XRD) - The drug is crystalline or amorphous/ Polymorphism of the drug can be identified too/
10. Solubility Studies: Solubility of NDDS can be determine which can be compare with pure drug. Whether the solubility is enhanced or not that can be calculated.
11. Contact angle measurement: Wettability of the NDDS in water can be determined which in turn gives idea about the solubility.
12. *In-vitro* drug release - For carrying out the drug release study it is desirable to select a dissolution medium which mimics physiological conditions of the body. Also the medium should be able to maintain sink conditions throughout the study.
13. Moisture content - Since NDDS will be spray dried or lyophilized. It is important to know the moisture content in dry powder as it can affect the assay of drug and efficacy too.
14. Aerodynamic properties: Particle size is one of the important parameter while giving formulation into pulmonary route. Thus behavior of particles should be determined as the
15. Powder flow properties: Bulk density, tapped density, Carr`s index, Hausner ratio, Angle of repose
16. Rheology study: The stability of nanosuspension can be determined if there is change in the viscosity of nanosuspension.

17. Sedimentation parameters: Flocculated or deflocculated suspension can be determined based on the sedimentation volume.

E. Efficacy Studies:

1. Cytotoxicity test on cell lines on A 549 cells and on mycobacterium strains.,
2. Drug-susceptibility testing.
3. MDR or XDR analysis
4. *In-vitro* lung deposition evaluation using twin stage impinger
5. *In-vitro* lung deposition evaluation using Anderson cascade impactor

F. *In-vivo* Study:

1. *In-vivo* lung deposition study.
2. To study pharmacokinetic parameters and serum albumin concentration.

G. Stability studies:

As per ICH Guidelines, overall the nano/microsystems will be evaluated in 3 conditions.

Sr. No.	**Conditions**	**Period**
1	5°C ± 3°C	6 months
2	25°C ± 2°C/60% RH ± 5% RH	6 months
3	30°C ± 2°C/65% RH ± 5% RH	6 months

10 Statistical Plan

Activity	1-6 months	6-12 Months	12-18 months	18-24 Months	24-30 months	30-36 months
Literature Survey						
Preformulation Studies						

Analytical Method Development						
Formulation, development and Optimization						
Optimization of formulation						
Characterization of optimized formulation						
Cell lines studies						
Animal Studies						
Stability studies						
Statistical Analysis, Data Interpretation and Conclusions						
Publishing Research and submitting data						

11. Limitations of the Study:

It is difficult to commercialize these technologies for use in clinical settings, partly because there is no efficient, scalable manufacturing process available. Additionally, there aren't many commercially accessible lipids that exhibit the requisite phase behavior.

12 Expected Outcomes of Study

- Formulation of an efficient nano/microcarrier system for antitubercular drug with improved delivery i.e. highest drug concentration at target sites and improve solubility as well as bioavailability.
- Developing an optimized and stable oral formulation for treatment of multidrug resistant tuberculosis.
- Efficacy of drug can be studied when given orally and pulmonary.

- Formulation of a carrier system which will overcome the drawbacks of conventional anti-tubercular formulations available currently like dose dependent toxicity and side effects

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